

## **Exhibit 2**

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## Antigen-specific suppressor T lymphocytes in man.

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The cellular signals that lead to activation of suppressor T cells (Ts) as opposed to cytotoxic T cells (CTL) are unknown. This review describes an *in vitro* suppressor-induction system developed by us to characterize interactions among various T cells leading to the development of antigen-specific suppression. In this system, antigen-specific CD4+ inducer T cells are first activated with antigen-presenting cells (APC). Antigen-primed CD4+ inducer cells are then cultured with fresh autologous CD8+ T cells in the absence of the priming antigen. CD8+ T cells isolated from this culture suppress the proliferative response of autologous CD4+ T cells to the priming antigen only. The activated CD8+ Ts lyse neither APC nor antigen-primed CD4+ inducer T cells and can be distinguished from their CD8+CD28+ CTL counterpart by their lack of expression of the CD28 molecule. Furthermore, the ability to induce CD8+ Ts is restricted to antigen-primed CD4+CD29+CD45R-p80+ (Leu8+) T cells.

Antibody-mediated inhibition experiments suggest the involvement of CD3/TCR and class I MHC molecules on the surface of CD4+ inducer T cells and the CD2, CD3/TCR, CD8, and CD11a/CD18 molecules on the surface of CD8+ Ts during both the induction and the effector phase of Ts function. Furthermore, compatibility at the class I MHC genes between CD8+ Ts and CD4+ antigen-reactive T cells is required for effective suppression of CD4+ T cells. Together, these results suggest that human antigen-specific CD8+ Ts employ the TCR complex to recognize TCR and class I MHC molecules on the surface of autologous CD4+ inducer T cells during the induction and effector phases of Ts function, and the apparent antigen specificity of suppression reflects specificity for antigen receptors on CD4+ antigen-reactive T cells. This may be a common mechanism by which antigen-specific suppression is accomplished.

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### Related Links

Immunoregulatory T lymphocytes in man. Soluble antigen-specific suppressor-inducer T lymphocytes are derived from the CD4+CD45R-p80+ subpopulation. [J Immunol. 1987] PMID:2887618

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Induction of xenoreactive CD4+ T-cell anergy by suppressor CD8+CD28- T  
cells. [Transplantation. 2000] PMID:10798745

Nonantigen specific CD8+ T suppressor lymphocytes originate from CD8+CD28- T  
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